

The University of Chicago

SOME SUBSTITUTED PYRIMIDINES

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE
PHYSICAL SCIENCES IN CANDIDACY
FOR THE DEGREE OF DOCTOR OF
PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1933

By

ELEANOR RACHEL BARTHOLOMEW

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ACKNOWLEDGMENT

The author wishes to express her sincere appreciation and gratitude to Professor Julius Stieglitz, under whose direction this problem was done, and to Dr. E. W. Lowe, for his assistance.



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SOME SUBSTITUTED PYRIMIDINES

Compounds containing the group $-CR_1R_2.CO.NH-$, where R_1 and R_2 are alkyl radicals, tend to exhibit hypnotic properties when introduced into the human organism. Typical of such compounds are the substituted barbituric acids, which have the general formula, $CO.NH.CO.CR_1R_2.CO.NH$. The usefulness of the barbituric acids is impaired by their tendency to produce skin eruptions and other signs of toxic action when administered to some persons. This is especially true of luminal (phenyl ethyl barbituric acid), a substance widely used to control epileptic seizures.

Investigations are now in progress in this laboratory, under the direction of Professor Stieglitz, to discover a substance of high hypnotic power and low toxicity. In the course of this work a large number of substituted uracils have been studied and this paper is concerned with the preparation of a few of these compounds.

A number of attempts, so far unsuccessful, have been made¹ to prepare a 5,5-dialkylated uracil of the formula, $HN.CO.N:C(CH_3).C(R_1R_2).CO$. The general procedure in these attempts has been to try to condense an α -dialkylacetoacetic ester with urea, or some urea derivative such as thiourea, guanidine, or an alkyl isourea. Since the desired condensations failed to take place, it was decided to try similar experiments

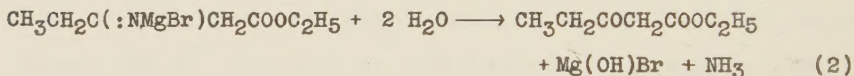
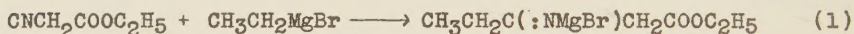
¹E. W. Lowe, unpublished work.

with other β -keto esters. The work discussed in Experimental Part I of this thesis describes various attempts to prepare propioacetic ester in good yields. It was intended to alkylate this ester in the two alpha positions and condense the product with urea or a urea derivative. However, practical yields were not obtained, and this phase of the work was abandoned in favor of the preparation of the 5-ampylpyrimidines described in Experimental Part II.

I

The literature contains two methods for the preparation of propioacetic ester, both of which were tried and found to be unsatisfactory.

Blaise¹ and Breckpot² prepared the ester from ethyl cyanoacetate as shown in the following equations:



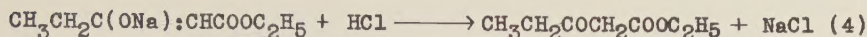
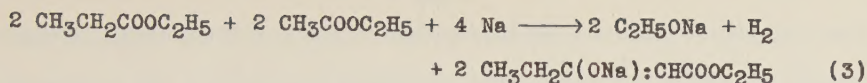
The maximum yield obtained by this process was ten per cent of the calculated amount. Since the preparation of large amounts of ethyl cyanoacetate is in itself a tedious and expensive process, the method was abandoned. However, it gave the best results of all the methods tried.

Wahl and Doll³ obtained the ester by the condensation of ethyl propionate with ethyl acetate according to the equations:

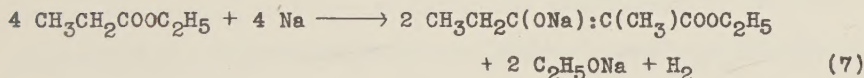
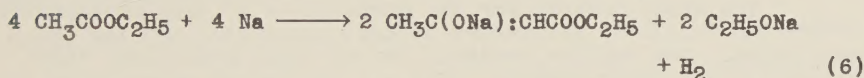
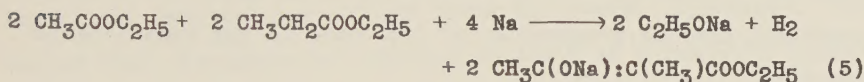
¹Blaise, Compt. rend. 132, 978, (1901).

²Breckpot, Bull. soc. chim. Belg. 32, 386, (1923).

³Wahl and Doll, Bull. soc. chim. (4) 13, 265, (1913); Wahl, Compt. rend. 152, 95, (1911); Ann. chim. (8) 23, 545, (1911).

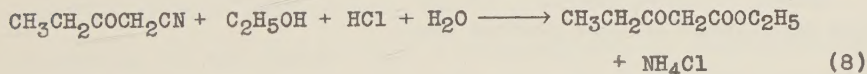


It is evident from a consideration of reaction (3) that in addition to ethyl propioacetate, three other products may be formed; namely, ethyl α -methyl acetoacetate, ethyl acetoacetate, and ethyl α -methyl propioacetate. The equations for the formation of these products are:



After a number of trials, ethyl acetoacetate was found to be the chief product of the reaction. Only minute quantities of ethyl propioacetate were obtained.

Attempts were made to prepare propioacetonitrile which, if obtained, could be esterified to give ethyl propioacetate according to the equation:

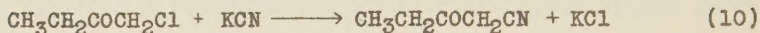
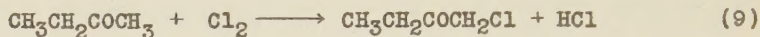


The only method given in the literature for the preparation of propioacetonitrile was that of Henry¹ and Reymenant² who reported

¹L. Henry, Bull. acad. roy. Belg. 1900, 57.

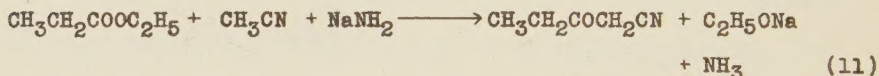
²Reymenant, *ibid.*, 1900, 724.

poor yields. They prepared propioacetonitrile from methyl ethyl ketone according to the following equations:



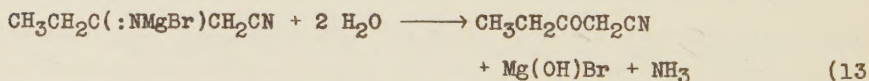
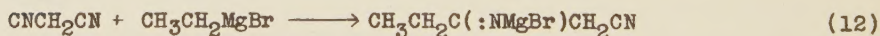
In the reaction shown in equation (9) the reported yield of the desired product was only 33 per cent of the calculated amount. Therefore, it was considered that the yield of ethyl propioacetate finally obtained by this process would be so small as to be impractical for the preparation of the ester in any considerable quantity.

Two other methods for the preparation of propioacetonitrile were tried. One was the condensation of ethyl propionate with acetonitrile, the equation for which is:



It was found that no propioacetonitrile could be obtained from this reaction. Instead, β -iminobutyronitrile seemed to be the chief product.

The other attempt to prepare propioacetonitrile as a means of obtaining the desired ester in good yields, was the condensation of malonyl dinitrile¹ with ethyl magnesium bromide. The equations for this process are:



¹Hesse, Am. Chem. J. 18, 746, (1896).

When malonyl dinitrile was treated with the Grignard reagent (Equation 12) a vigorous reaction took place, but none of the desired propioacetonitrile could be obtained from the reaction product. At this point it was decided to abandon this phase of the work and to prepare, instead, the 5-amyl uracils which are described below.

II

Of the various theories advanced to explain the mechanism of hypnotic activity of organic substances, the one proposed by Meyer¹ and Overton² has brought forth the fewest objections. It states that the degree of narcotic activity of a compound depends upon its mechanical affinity for fat-like substances on the one hand, and for body constituents, especially water, on the other. An approximate measure of the ratio between these two affinities may be determined from the distribution coefficient of the substance between olive oil and water. Tabern and Shelberg³ have recently published data supporting the theory that there is a definite parallelism between the distribution coefficient and hypnotic activity. Of the di-alkyl barbituric acids studied, they found that those which had the highest distribution ratio (olive oil to water) exhibited the greatest hypnotic power. In some work done in this laboratory, it has been found that 4-methyl-5-ethyluracil, $\text{HNCONHC}(\text{CH}_3):\text{C}(\text{C}_2\text{H}_5)\text{CO}$, though possessing a very low distribution coefficient, showed a slight sedative action. Therefore, it was thought that a compound such as 4-methyl-5-amyl

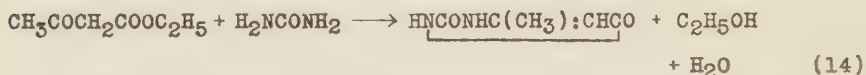
¹Meyer, Arch. f. exp. Path. u. Pharm., 42, 109, (1899); 46, 338, (1901); Baum, ibid., 42, 119, (1899).

²Overton, Studien uber die Narkose. Jena, 1901.

³Tabern and Shelberg, J. Am. Chem. Soc. 55, 328, (1933).

uracil, $\text{HNCONHC}(\text{CH}_3):\text{C}(\text{C}_5\text{H}_{11})\text{CO}$, which would have a higher distribution coefficient, would show a greater sedative power. Accordingly, a number of n-amyl and isoamyl derivatives of uracil were prepared. The physiological action of these compounds is now being determined and will be described in later publications.

Uracil was first synthesized by Lengfeld and Stieglitz,¹ in 1893, by heating β -ureidopropionic acid with hydrochloric acid. Behrend² first prepared a 4-substituted uracil, namely, 4-methyluracil, by the condensation of ethyl acetoacetate with urea according to the equation:



Fischer and Roeder³ also used urea and β -keto-esters for the preparation of 4-alkyl uracils. Behrend found, however, that α -substituted acetoacetic esters would not undergo analogous condensations with urea.

Acetoacetic ester has been condensed with the stronger bases guanidine^{4,5} and thiourea.⁵ α -Methyl and ethyl β -keto-esters have been condensed with these substances^{6,7} and with pseudo-thiourea.⁸ The yields obtained with pseudo-thiourea and

¹Stieglitz, Am. Chem. J. 15, 221, and 517, (1893).

²Behrend, Ann. 229, 5, (1885); Behrend and Roosen, ibid., 251, 238, (1889).

³Fischer and Roeder, Ber. 34, 3751, (1901).

⁴Curatolo, Gazz. chim. ital. 20, 585, (1890).

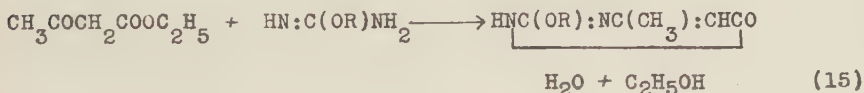
⁵Behrend, loc. cit.

⁶Byk, Ber. 36, 1915, (1903).

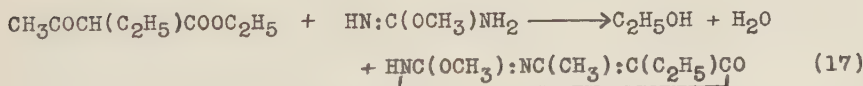
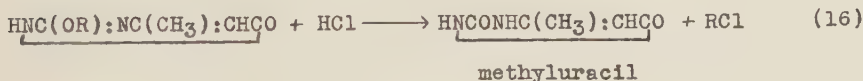
⁷Johnson and Bailey, J. Am. Chem. Soc. 35, 1007, (1913); Johnson and Hill, ibid., 36, 364, (1914).

⁸Wheeler and Merriam, Am. Chem. J. 29, 478, (1903); Johnson and McCollum, J. Biol. Chem. 1, 437, (1905).

guanidine as condensing agents are poor. Use of thiourea involves the removal of sulphur, which is both a difficult and malodorous process. A simple method for the preparation of substituted uracils from β -keto-esters was devised in this laboratory under the direction of Stieglitz when Bruce¹ condensed acetoacetic ester and its α -ethylated derivative with alkyl isoureas² according to the following equations:

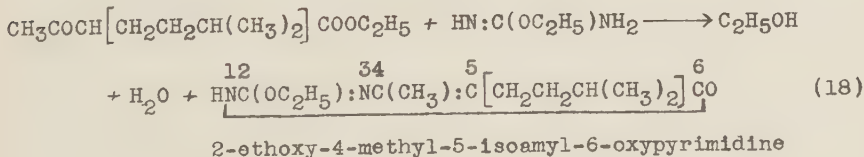


where R represents the alkyl radicals CH_3 and C_2H_5 .



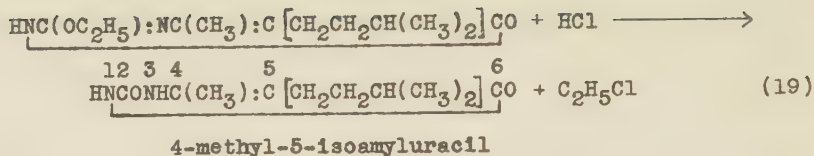
This process was the method used in the present work for the preparation of the desired uracils.

4-Methyl-5-isoamyluracil was prepared from ethyl isourea and ethyl α -isoamylacetoacetate according to the following equations:



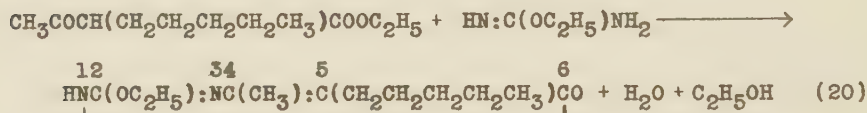
¹Bruce, J. Am. Chem. Soc. 26, 419, and 449, (1904).

²Stieglitz and McKee, Ber. 32, 1494, (1899); 33, 807. 1517, (1900); McKee, Am. Chem. J. 26, 209, (1901).

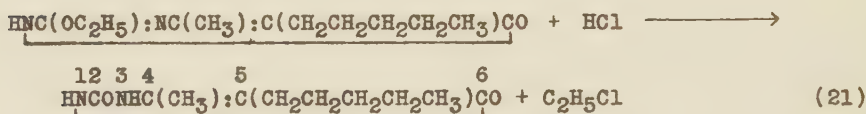


The distribution coefficient of 2-ethoxy-4-methyl-5-isoamyl-6-oxypyrimidine is 2.93 at 25° and that of 4-methyl-5-isoamyluracil is 1.74 at 25°.

4-Methyl-5-n-amyluracil was similarly prepared from ethyl isourea and α-n-amylacetoacetic ethyl ester. The equations for the process are:



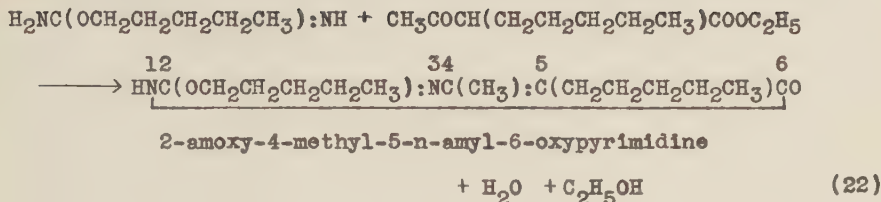
2-Ethoxy-4-methyl-5-n-amyl-6-oxypyrimidine has a distribution coefficient of 1.33 at 25°.



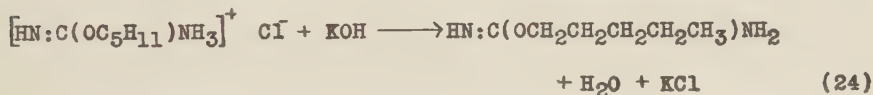
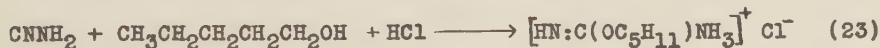
4-Methyl-5-n-amyluracil has a distribution coefficient of 0.64 at 25°.

Since the 2-ethoxy derivatives of the 5-amylated uracils had greater distribution coefficients than the corresponding uracils, it was decided to try the effect of an amoxy group in place of the ethoxy group. It was hoped that by this substitution the distribution coefficient and hypnotic power would be increased. In order to prepare a substituted pyrimidine with an amoxy group in the 2-position, n-amyl isourea was prepared and condensed with ethyl α-n-amylacetoacetate according to the

equation:



Amyl isourea was prepared by the method given by Stieglitz and McKee¹ for the preparation of ethyl isourea and used by Basterfield² for the preparation of other isoureas. The preparation is represented by the following equations:



A large excess of n-amyl alcohol (10 moles to 1 mole of cyanamide) was found to give the best results both as to yield and as to time required. Details will be found in the experimental part.

n-Amyl isourea was condensed with α-n-amylacetoacetic ethyl ester to form 2-amoxy-4-methyl-5-n-amyl-6-oxypyrimidine which has a distribution coefficient of 0.86 at 25°.

The work of Tabern and Shelberg³ has shown that the dialkyl barbituric acids which have a distribution coefficient (between oil and water) of approximately four, are the most efficient hypnotics. The distribution coefficients of the 5-amyl

¹Stieglitz and McKee, loc. cit.; McKee, loc. cit.

²Basterfield and Whelen, J. Am. Chem. Soc. 49, 3177, (1927); Basterfield and Powell, Can. J. Research 1, 261, (1929).

³Tabern and Shelberg, loc. cit.

uracils described in this paper are here tabulated together with those of several barbituric acids.

Uracil	Dist. coef- ficient	Barbituric Acid	Dist. coef- ficient	Eff.* Rat.
		Ethyl 1-methyl butyl (nembutal)	4.4	+++
2-Ethoxy-4-methyl-5-1- amyl-6-oxypyrimidine	2.93	1-Amyl ethyl (Amytal)	2.895	+++
4-Methyl-5-1-amyluracil	1.74	n-Amyl ethyl	2.92	+++
2-Ethoxy-4-methyl-5-n- amyl-6-oxypyrimidine	1.33	sec.-Butyl ethyl	1.36	+++
4-Methyl-5-n-amyluracil	0.64	Phenyl ethyl (Luminal)	1.34	++
2-Amoxy-4-methyl-5-n- amyl-6-oxypyrimidine	0.86	Ethyl 1-propyl (Ipral)	0.73	+
		Diethyl (Barbital)	0.214	+

*Efficiency rating and distribution coefficients of the barbituric acids are from the table of Tabern and Shelberg.¹

A comparison of the coefficients of the five pyrimidine derivatives shows that the derivatives containing an ethoxy group have larger coefficients than the uracils themselves. It also shows that the introduction of an amoxy group into the molecule did not increase the coefficient over that of the ethoxy derivative as was expected, but rather that it decreased the value of the coefficient.

If the theory of Meyer and Overton holds for these compounds it can be seen that the uracils listed above should have a hypnotic power approximately equal to that of Amytal or Luminal.

¹Tabern and Shelberg, loc. cit.

Whether this is true will be disclosed when the necessary pharmacological tests are completed.

EXPERIMENTAL PART

I

ATTEMPTS TO PREPARE ETHYL PROPIOACETATE IN GOOD YIELDS

The Reaction of Sodium Amide on Ethyl Propionate and Acetonitrile.- Ethyl propioacetate, $\text{CH}_3\text{CH}_2\text{COCH}_2\text{COOC}_2\text{H}_5$, is reported to have been prepared in very small amounts by several methods. In the search for a practical method of preparation, an attempt was made to prepare propioacetonitrile which could then be esterified. The method tried was the condensation of ethyl propionate with acetonitrile by means of sodium amide.

To a suspension of 4.5 g. of powdered sodium amide in 100 cc. of anhydrous ether in an atmosphere of nitrogen was added (dropwise, with stirring) 4.1 g. of acetonitrile. A white solid precipitated and the mixture was refluxed for one hour. Then ethyl propionate (10.2 g.) was added to the mixture and it was refluxed again for one hour. It was allowed to stand overnight; the white solid did not dissolve until water was added to the mixture. The ether layer was separated, washed with dilute hydrochloric acid to remove ammonia and dried over calcium chloride. When distilled it was found to be only ether. The aqueous solution of the solid salt was acidified with hydrochloric acid and extracted with ether. All of this extract distilled below 85° , whereas propioacetonitrile has a boiling point of $164-5^\circ$.¹

¹Henry, loc. cit.

The procedure was then modified. Instead of refluxing the acetonitrile with the sodium amide before the addition of the ethyl propionate, a mixture of acetonitrile and ethyl propionate in ether was added to a suspension of sodium amide in ether. The results were the same as in the previous attempt; so this method of preparation of propioacetonitrile was abandoned.

The Reaction of Malonyl Dinitrile and Ethyl Magnesium

Bromide.- An attempt was next made to prepare propioacetonitrile from malonyl dinitrile by means of a Grignard reagent. Ethyl magnesium bromide (44 g.) was prepared in an ether solution in the usual way. This was then added, drop by drop with stirring, to 24 g. of malonyl dinitrile in an ether solution. As each drop of Grignard reagent was added much gas was evolved and a greenish white, gummy mass was formed. After all the Grignard reagent had been added, the mass was decomposed with water and extracted with both ether and benzene. The benzene extracted nothing and the ether extraction yielded only a small amount of a yellow-brown solid, whose composition was not determined, but none of the imido propioacetonitrile, $C_2H_5C(:NH)CH_2CN$. The method was not successful, and the reaction was not studied further.

The Reaction of Ethyl Cyanoacetate and Ethyl Magnesium

Bromide.- Ethyl propioacetate was prepared by the method of Blaise¹ and of Breckpot² from ethyl cyanoacetate and ethyl magnesium bromide. The Grignard reagent was prepared in the usual way from 72 g. of ethyl bromide and 16 g. of magnesium powder, and to it, drop by drop with vigorous stirring, was added 50 g. of ethyl cyanoacetate. The addition of cyanoacetate caused the

¹Blaise, loc. cit.

²Breckpot, loc. cit.

evolution of gas with the formation of a yellow-green mass, which became more and more difficult to stir, and finally solidified. It was then decomposed with water; which was a difficult process, for the hard mass was not easily broken up. The water solution was acidified with hydrochloric acid and extracted with ether. The ether extracts were fractionally distilled under reduced pressure. Three fractions were collected at 11-12 mm. pressure: (1) of boiling point 88-105°, (2) of b. pt. 105-130°, and (3) of b. pt. 130-210°. Fraction (1) gave the standard red color test with ferric chloride for keto-esters and weighed 7 g. Since this was only 10 per cent of the calculated yield, the method was not considered suitable for the preparation of this ester in the large amounts necessary. It gave, however, the best results of all the methods used.

The Reaction of Sodium on Ethyl Acetate and Ethyl Propionate.- Preparation of ethyl propioacetate in greater yields was next attempted by the method of Wahl and Doll,¹ who claimed to get 20 per cent yields. One mole (102 g.) of ethyl propionate was placed in a one liter round bottom flask which was equipped with a reflux condenser and mechanical stirrer. To it was added 70 g. (3 mol.) of finely shaved sodium in 1 g. portions, and 265 g. (3 mol.) of ethyl acetate in 5 cc. portions. The flask was heated on an oil bath at 100-105°, at which temperature the reaction took place most readily. A gram of sodium was added only after the previous one had disappeared. The reaction took about 17-18 hours. The semi-solid mass which resulted stood overnight and the next day was decomposed with dilute hydrochloric acid. The oil which separated was taken up with ether and the aqueous

¹Wahl and Doll, loc. cit.

phase was extracted with ether. The ethereal solution was then washed with sodium carbonate and then dried with calcium chloride and the ether was evaporated. The residual oil fractionally distilled at 10-11 mm. pressure gave 87 g. of a fraction which had a boiling point range of 70 to 88°. This was a mixture of esters which were difficult to separate by fractionation. There is the possibility of the formation of four keto-esters by this process, namely, ethyl propioacetate, ethyl α -methyl acetoacetate, ethyl acetoacetate, and ethyl α -methyl propioacetate.

Dieckmann¹ has reported that when alkylated keto-esters are heated with alcoholic sodium ethylate they are alcoholized into ethyl acetate and the corresponding alkyl ester. Such a treatment of the above mixture of esters should, then, decompose the α -alkylated keto-esters (ethyl α -methyl propioacetate and ethyl α -methyl acetoacetate) if they are present in the mixture. Therefore, 17 g. of the mixture was heated for two hours with sodium ethylate in an alcoholic solution (2.5 g. of sodium was dissolved in 60 cc. of absolute ethanol). This mixture was then acidified, the alcohol distilled off, and the residue extracted with ether. When fractionally distilled it was found that the esters had the same boiling point range as before the treatment, which indicated that either none of the two possible α -alkylated keto-esters was present or that they were not destroyed by the treatment. Therefore, this treatment of the esters with sodium ethoxide was discontinued.

Two hundred grams of the mixture of esters was fractionally distilled through a Peters and Baker column.² The fractions obtained at 746 mm. pressure were: (1) b. pt. 160-170°, 63 g.;

¹Dieckmann, Ber. 33, 2670, (1900).

²Peters and Baker, J. Ind. Eng. Chem. 18, 69, (1926).

(2) b. pt. 177-182°, 83 g.; (3) b. pt. 182-185°, 5 g.; and (4) a tar left in the distilling flask. The boiling points of the four possible esters are: Ethyl acetoacetate 180-181°,¹ ethyl α -methyl propioacetate 187°,² ethyl propioacetate 191°,³ and ethyl α -methyl propioacetate 196-7°. ⁴ Therefore, the boiling points of the fractions indicate that the material was probably nearly all acetoacetic ester with possibly only a very small amount of propioacetic ester in the third fraction.

The Reaction of Sodium Ethoxide on Ethyl Acetate and Ethyl Propionate.- The preparation of the desired ester was attempted by a modification of Wahl's procedure. Molar quantities of sodium, ethyl acetate, and ethyl propionate with a few drops of absolute ethanol were used instead of three moles of sodium and ethyl acetate to one mole of ethyl propionate. Ten drops of absolute ethanol were added to 12 g. (one half mole) of sodium wire in ether. The flask was warmed on the steam bath and a mixture of 44 g. (one half mole) of ethyl acetate and 51 g. (one half mole) of ethyl propionate was gradually added. The ether was kept at the boiling point and apparently a reaction took place. Decomposition with dilute hydrochloric acid and extraction with ether yielded only a small amount of material. This when distilled was found to have a low boiling point range which would correspond to the boiling points of the original esters. No propioacetic ester was obtained.

no practical method for the preparation of large amounts of ethyl propioacetate was found.

¹Schiff, Ber. 19, 561, (1886); Bruhl, Ann. 203, 27, (1880).

²Geuther, Zeit. f. Chem. 1866, 7.

³Boeseken, Rec. trav. chim. 15, 161, (1896).

⁴Hellon and Oppenheim, Ber. 10, 699, (1877); Hamonet, Bull. soc. chim. (3) 2, 338, (1889); Zeltner, Ber. 41, 589, (1908).

II

PREPARATION OF 5-AMYL PYRIMIDINES

Preparation of α -Isoamylacetoacetic Ethyl Ester,

$\text{CH}_3\text{COCH} [\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2] \text{COOC}_2\text{H}_5$. - The methods given in the literature¹ for the preparation of α -isoamylacetoacetic ethyl ester were tried and found to be unsatisfactory for the preparation of the ester in large quantities. It was found that better results could be obtained by the heating of ethyl acetoacetate and isoamyl bromide under pressure in the presence of alcoholic sodium ethylate.

Sodium (11.5 g., one half mole) was dissolved in 200 cc. of absolute ethanol in a 500 cc. round bottom flask which was equipped with a reflux condenser. One half mole (65 g.) of ethyl acetoacetate was added to the solution and the mixture was well shaken. Eighty-three grams (10 per cent excess) of isoamyl bromide (b. pt. 118-122°) was then added to the mixture which was then poured into a large test tube (2x15 inches). This tube was placed in an iron bomb (made of cast iron pipe with a screw cap), which was then sealed with the aid of plumber's cement. The iron bomb containing the reaction mixture was heated in an oil bath at 110-115° for one and one half hours. This temperature must be exact, as the reaction does not take place at lower temperatures, and at higher temperatures alcoholysis of the alkylated ester takes place. At the end of the heating period the bomb was removed

¹Bischoff, Ber. 28, 2627, (1895); Locquin, Bull. soc. chim. (3) 31, 759, (1904); Peters, Ber. 20, 3322, (1887).

from the hot oil bath, cooled overnight and opened the next day. The alcohol was evaporated on a steam bath, and the residual oil was shaken with water, which dissolved the sodium bromide and also hydrolyzed the sodium salt of any unchanged acetoacetic ester. The oil was separated and the water layer extracted with ether three or four times. These ether extracts were added to the original oil and the ether was evaporated on the steam bath. The residual oil was then fractionally distilled. α -Isoamylacetoacetic ethyl ester according to White¹ has a boiling point of 228°. The fraction of boiling point 225-230° at 750 mm. pressure was collected and weighed 60 g., which was 60 per cent of the calculated yield.

Preparation of α -n-Amylacetoacetic Ethyl Ester,

$\text{CH}_3\text{COCH}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)\text{COOC}_2\text{H}_5$.- Ponzio and Prandi² prepared α -n-amylacetoacetic ethyl ester from sodium acetoacetic ethyl ester and n-amyl iodide. In the present work it was prepared from the bromide by the same method as that used for the preparation of α -isoamylacetoacetic ethyl ester, except that it was necessary to raise the reaction temperature to 115-120°. Fractional distillation of the oil gave a fraction of boiling point 240-245° at 744 mm. pressure, which was 60 per cent of the calculated yield. Ponzio and Prandi gave the boiling point of this ester as 242-244° at 738 mm. pressure.

2 - Ethoxy - 4 - Methyl - 5 - Isoamyl - 6 - Oxy pyrimidine,

$\text{HNC}(\text{OC}_2\text{H}_5):\text{NC}(\text{CH}_3):\text{C}[\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2]\text{CO}$.- Equimolecular quantities (one half mole) of ethyl isourea (prepared by the method of

¹Eileen White, J. Chem. Soc. 1928, 1413.

²Ponzio and Prandi, Gazz. chim. ital. 28, II, 280, (1898).

McKee¹ as modified by Terre²) and α -isoamyl acetoacetic ethyl ester were mixed in a glass evaporating dish and allowed to stand in an evacuated desiccator over sulphuric acid and solid potassium hydroxide. A white solid began to appear after a few hours and at the end of two or three days the desiccator was opened and the mixture was stirred. At this point it was advisable to renew the sulphuric acid before re-evacuation of the desiccator. At the end of four days the mixture was taken out of the desiccator and the crystals were collected on a filter with suction. The filtrate was replaced in the vacuum desiccator and allowed to stand. After it had stood an additional four days, maximum condensation seemed to have taken place. In previous experimental work it has been found that the application of heat does not aid the condensation. The solid was collected on a filter with suction and added to the first crop. This impure 2-ethoxy-4-methyl-5-isoamyl-6-oxypyrimidine was triturated with a small volume of acetone and the undissolved residue was again brought upon a filter. It was then recrystallized from 50 per cent ethanol and was found to have a melting point of 98-99° (all melting points given in this paper are corrected.) Micro-analyses for nitrogen gave the following results:

Sub.: 3.798 mg., N₂, 0.429 cc. at 304° K. and 746 mm.

3.024 mg., N₂, 0.330 cc. at 297.5° K. and 747 mm.

Calc. for C₁₂H₂₀N₂O₂: N, 12.50 %.

Found: N, 12.46 %, 12.69 %.

Eleven grams of the pure product was obtained, which was only 9 per cent of the calculated yield. The filtrate from the condensation mixture was boiled with dilute hydrochloric acid where-

¹McKee, loc. cit.

²Terre, Master's Dissertation, University of Chicago, 1932.

upon 19 g. of 4-methyl-5-isoamyluracil (see the following paragraph) separated. Nineteen grams of the uracil is equivalent to 24 g. of the ethoxy derivative. Therefore, the condensation must have taken place to the extent of 31 per cent, but, due to the solubility of the 2-ethoxy pyrimidine in the oily reaction mixture, it was possible to isolate only one third of the product. It was found to be soluble in all of the common organic solvents. The solubility in water was found to be 0.041 g. per 100 cc. of water at 25°. The distribution coefficient between olive oil and water was determined by the method of Tabern and Shelberg.¹ Equal volumes of oil and saturated water solution were shaken together until equilibrium was established. Analyses of the aqueous phase were made by the Kjeldahl method. The distribution coefficient was found in this manner to be 2.93 at 25°.

4 - Methyl - 5 - Isoamyluracil,

$\text{HNCONHC}(\text{CH}_3):\text{C}[\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2]\text{CO}$.- Two grams of 2-ethoxy-4-methyl-5-isoamyl-6-oxypyrimidine were dissolved in hot dilute (1:3) hydrochloric acid. When boiled for a few minutes ethyl chloride was evolved and a pearly, white precipitate of 4-methyl-5-isoamyluracil appeared. The solution was then cooled and the precipitate was collected on a filter with suction. On recrystallization from 50 per cent ethanol it melted at 248.5-249.5°. Micro-analyses for nitrogen gave the following results:

Sub: 3.325 mg., N_2 , 0.408 cc. at 287° K. and 749 mm.

4.060 mg., N_2 , 0.510 cc. at 296° K. and 750 mm.

Calc. for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_2$: N, 14.28 %.

Found: N, 14.29 %, 14.30 %.

Yield, 1.4 g., or 80 per cent of the calculated amount. The

¹Tabern and Shelberg, loc. cit.

compound is only slightly soluble in benzene but soluble in most of the other common organic solvents. The solubility in water was found to be 0.039 g. per 100 cc. of water at 25°. The distribution coefficient between olive oil and water was found to be 1.74 at 25°.

2 - Ethoxy - 4 - Methyl - 5 - n-Amyl - 6 - Oxypyrimidine,

$\text{HNC}(\text{OC}_2\text{H}_5):\text{NC}(\text{CH}_3):\text{C}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)\text{CO}-$ Equimolecular quantities (one half mole) of ethyl isourea and n-amylacetoacetic ethyl ester were mixed in a glass evaporating dish and allowed to stand in an evacuated desiccator over sulphuric acid and solid potassium hydroxide. A white solid began to appear after a few hours. At the end of two days the desiccator was opened, the mixture was stirred, and the sulphuric acid was renewed. After seven days the mixture was taken out of the desiccator and the precipitate was collected by suction on a filter. The filtrate was replaced in the vacuum desiccator for further condensation. After four more days condensation seemed to be complete. The precipitate was collected on a filter and added to the first crop. This solid, to which oil still adhered, was then triturated with 100-150 cc. of acetone and again separated by filtration. After this treatment the 2-ethoxy-4-methyl-5-n-amyl-6-oxypyrimidine could readily be recrystallized from 50 per cent ethanol. It had a melting point of 90-90.5°. Micro-analyses for nitrogen gave the following results:

Sub: 3.298 mg., N_2 , 0.368 cc. at 299° K. and 744 mm.

3.285 mg., N_2 , 0.366 cc. at 297° K. and 744 mm.

Calc. for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_2$: N, 12.50 %.

Found: N, 12.48 %, 12.54 %.

The yield of the pure product was 23 g. or 20 per cent of the

calculated amount. However, if the oily filtrate from the condensation product was boiled with dilute hydrochloric acid, 17 g. of 4-methyl-5-n-amyluracil (see the following paragraph) was obtained. This showed that the reaction had taken place to the extent of 40 per cent of the calculated amount and that it was possible to isolate only one half of the product. It is soluble in the common organic solvents. The solubility in water was found to be 0.018 g. per 100 cc. of water at 25°. The distribution coefficient between olive oil and water is 1.33 at 25°.

Preparation of 4 - Methyl - 5 - n-Amyluracil,

$\text{HNCONHC}(\text{CH}_3):\text{C}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)\text{CO}$.- Two grams of 2-ethoxy-4-methyl-5-n-amyl-6-oxypyrimidine was dissolved in hot dilute (1:3) hydrochloric acid. When the solution was boiled for a few minutes, ethyl chloride was evolved and a pearly, white precipitate of 4-methyl-5-n-amyluracil separated. The solution was then cooled. The precipitate was collected on a filter. On recrystallization from 50 per cent ethanol it melted at 235.5-236.5°.

Micro-analyses for nitrogen gave the following results:

Sub: 3.703 mg., N_2 , 0.464 cc. at 298° K. and 752 mm.

3.350 mg., N_2 , 0.422 cc. at 298° K. and 752 mm.

Calc. for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_2$: N, 14.28 %.

Found: N, 14.21 %, 14.29 %.

Yield, 1.5 g., which was 85 per cent of the calculated yield. The uracil is soluble in the common organic solvents. The solubility in water was found to be 0.032 g. per 100 cc. of water at 25°. The distribution coefficient between olive oil and water is 0.64 at 25°.

n-Amyl Isourea Hydrochloride,

$\left[\text{HN:C(OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)\text{NH}_3 \right]^+ \text{Cl}^-$. - The hydrochloride of n-amyl isourea was prepared by the method of Stieglitz and McKee¹ and Basterfield² except that a smaller quantity (10 instead of 12 moles) of alcohol to one mole of cyanamide was used. It was found that if the proportion of alcohol to cyanamide was cut further (6 moles to 1), the time required for the completion of the reaction greatly increased. With 10 or 12 moles of alcohol to one of cyanamide the reaction took place in four hours, but with a 6:1 ratio the reaction took 84 hours for completion. When the amount of alcohol was cut to three moles, the reaction had not yet come to completion at the end of ten weeks.

Cyanamide (16.8 g. or 0.4 mole) was dissolved in 440 g. (4 moles) of n-amyl alcohol; into this solution, cooled in an ice-salt bath, was passed 15 g. (0.4 mole) of dry hydrogen chloride. If the mixture was shaken occasionally, the precipitate of cyanamide dihydrochloride, which had immediately appeared, dissolved in three hours. At the end of four hours the solution no longer gave a test for cyanamide with ammoniacal silver nitrate. The excess of n-amyl alcohol was distilled off under reduced pressure (1 to 2 mm.) on a water bath whose temperature was not allowed to rise above 45°. The viscous oil obtained was further dried in a vacuum desiccator over sulphuric acid and solid potassium hydroxide. It was never possible to get this mass to crystallize and no method of purification could be found. It was very soluble in water. Analyses for chlorine of this crude mass by Mohr's method gave the following results:

¹Stieglitz and McKee, loc. cit.; McKee, loc. cit.

²Basterfield, loc. cit.

Sub: 0.1609 g., AgNO_3 (0.0526 N), 17.15 cc.

0.2135 g., 22.70 cc.

Calc. for $\text{C}_6\text{H}_{15}\text{N}_2\text{OCl}$: Cl, 21.28 %.

Found: Cl, 19.88 %, 19.83 %.

n-Amyl Isoourea, $\text{HN:C}(\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)\text{NH}_2$. - The isoourea was prepared from its hydrochloride in the same manner as that used for ethyl isoourea by Terre.¹

Sixty-six grams (.4 mole) of n-amyl isoourea hydrochloride was placed in a 400 cc. beaker with 1 to 2 cc. of water. The viscous syrup was covered with 200 cc. of alcohol-free ether, and the whole cooled in an ice-salt bath. Two moles of powdered potassium hydroxide (112 g.) was added slowly to the mixture with constant stirring. The ether was poured off and the residue was extracted four times with more ether. The ether was evaporated and the residual oil dried in a vacuum desiccator over sulphuric acid and potassium hydroxide. The yield of pure, free base was 47 g., which was 90 per cent of the calculated yield. It was a clear liquid which had a boiling point of $100-101^\circ$ at 1 mm. pressure and $120-122^\circ$ at 5-6 mm. pressure. Micro-analyses for nitrogen gave the following results:

Sub: 1.475 mg., N_2 , 0.286 cc. at 302° K. and 747 mm.

1.404 mg., N_2 , 0.272 cc. at 300° K. and 745 mm.

Calc. for $\text{C}_6\text{H}_{14}\text{N}_2\text{O}$: N, 21.53 %.

Found: N, 21.59 %, 21.63 %.

2 - Amoxy - 4 - Methyl - 5 - n-Amyl - 6 - Oxypyrimidine,
 $\text{HNC}(\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3):\text{NC}(\text{CH}_3):\text{C}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)\text{CO}$. - Equimolecular quantities (one half mole) of n-amyl isoourea and α -n-amylaceto-

¹Terre, loc. cit.

acetic ethyl ester were mixed in a glass evaporating dish and allowed to stand in an evacuated desiccator over sulphuric acid and solid potassium hydroxide. The solution turned cloudy in a few minutes. The desiccator was opened, the mixture stirred, and the acid renewed every day or two. At the end of ten days it had become a stringy mass and no change took place if it was allowed to stand longer. It was impossible to separate the product by filtration. It was dissolved in a small volume of acetone and the resulting solution was cooled in an acetone-carbon dioxide bath. The white solid which separated was brought upon a filter which was surrounded by an acetone-CO₂ bath. This solid was found to be a mixture of two compounds. They could be separated by extraction of the mixture with about ten volumes of acetone which dissolved 2-amoxy-4-methyl-5-n-amyl-6-oxypyrimidine. When the acetone solution was cooled in an acetone-carbon dioxide bath the pyrimidine was precipitated. It was separated by filtration and recrystallized from 80 per cent ethanol. It crystallized in the form of glittering, white plates which had a melting point of 65-6°. Micro-analyses for nitrogen gave the following results:

Sub: 4.218 mg., N₂, 0.412 cc. at 309° K. and 740 mm.

3.272 mg., N₂, 0.306 cc. at 298° K. and 751 mm.

Calc. for C₁₅H₂₆N₂O₂: N, 10.52 %.

Found: N, 10.51 %, 10.59 %.

It was assumed that the solid left undissolved by the acetone extraction might be a salt of 2-amoxy-4-methyl-5-n-amyl-6-oxypyrimidine with some organic base such as the isourea itself. This assumption was made because the substance was easily converted into the pure pyrimidine. When it was dissolved in ethanol and dilute hydrochloric acid was added to the solution, the latter became slightly turbid. Water added to this alcoholic

olution caused the precipitation of a white crystalline solid which had a melting point of $65-6^{\circ}$. A melting point of the mixture of this solid and pure 2-amoxy-4-methyl-5-n-amyl-6-oxy-pyrimidine was the same, $65-6^{\circ}$, as that of the pure amoxy pyrimidine. This proved that the pyrimidine had been set free from this salt-like substance by hydrochloric acid. It was thought that the salt-like substance might be a salt of amyl isourea and 2-amoxy-4-methyl-5-n-amyl-6-oxy-pyrimidine, $C_{15}H_{25}N_2O_2$, $C_6H_{15}N_2O$. Such a compound would have a nitrogen content of 14.14 %. Micro-analyses of the substance gave the following data:

Sub: 2.172 mg., N_2 , 0.347 cc. at 306° K. and 743 mm.

2.862 mg., N_2 , 0.449 cc. at 300° K. and 744 mm.

Calc. for $C_{21}H_{40}N_4O_3$: N, 14.14 %.

Found: N, 17.44 %, 17.49 %.

It is evident that the substance which gave this analyses was not the pure salt shown in the above formula. A similar salt of the pyrimidine with urea itself, $C_{15}H_{25}N_2O_2 \cdot CON_2H_5$, would have a nitrogen content of 17.23%. The agreement with theory may be quite fortuitous since nothing further was done to determine the nature of the compound because the desired pyrimidine could readily be obtained from it. The yield of pure 2-amoxy-4-methyl-5-n-amyl-6-oxy-pyrimidine obtained from the above procedures was 22 g., which was 16 per cent of the calculated yield. The solubility in water was found to be 0.029 g. per 100 cc. of water at 25° . The distribution coefficient between olive oil and water was 0.86 at 25° .

SUMMARY

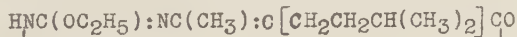
(1) The following methods of preparation of ethyl propionate were investigated with the object of making the ester on a large scale:

- (a) The reaction of sodium amide on ethyl propionate and acetonitrile.
- (b) The reaction of malonyl dinitrile and ethyl magnesium bromide.
- (c) The reaction of ethyl cyanoacetate and ethyl magnesium bromide.
- (d) The reaction of sodium on ethyl acetate and ethyl propionate.
- (e) The reaction of sodium ethoxide on ethyl acetate and ethyl propionate.

Of these methods, that of Blaise and of Breckpot (c) gave the best results with a yield of the ester of 10 per cent of the theoretical. However this was not considered a satisfactory method for the preparation of the ester in large quantities.

(2) The following pyrimidines were prepared and their solubilities and distribution coefficients were determined for a study of their possible pharmacological value as hypnotics:

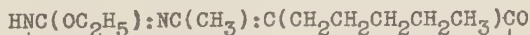
2-Ethoxy-4-methyl-5-isoamyl-6-oxypyrimidine



4-Methyl-5-isoamyluracil



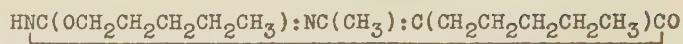
2-Ethoxy-4-methyl-5-n-amyl-6-oxypyrimidine



4-Methyl-5-n-amyluracil



2-Amoxy-4-methyl-5-n-amy-6-oxypyrimidine



(3) In the course of the investigation n-amy isburea and its hydrochloride were prepared and studied.

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